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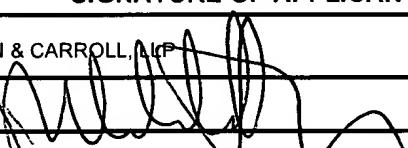
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## TRANSMITTAL FORM

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Art Unit	1643
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<input type="checkbox"/> Remarks Submitted herewith, in triplicate, is Appellant's Brief in furtherance of the Notice of Appeal filed June 5, 2006 and received in the U.S. Patent Office on June 7, 2006. Applicants believe no fee is required. Please charge any additional fees, including any fees necessary for extensions of time, or credit overpayment to Deposit Account No. 08-1290.		
<b>SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT</b>		
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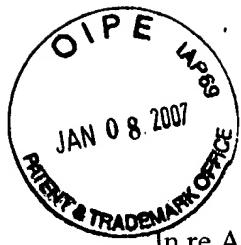
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PATENT  
Attorney Docket No. KNAUTHE-08713

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gabrielle Multhoff *et al.*

Serial No.: 09/646,835

Group No.: 1643

Filed: 01/11/01

Examiner: Christopher Yaen

Entitled: Use of Hsp70 Proteins

**APPELLANTS' BRIEF**  
**APPEAL NO.:**

Mail Stop Appeal Brief - Patents  
Commissioner for Patents and Trademarks  
P.O. Box 1450  
Alexandria, VA 22313-1450

**CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)**

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P.O. Box 1450  
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Dated: January 4, 2007

By:

  
Mary Ellen Waite

Sir or Madam:

This Brief is in furtherance of the Notice of Appeal filed June 5, 2006.

The fees required under § 1.17(h) and any required Petition for Extension of Time for filing this Brief and fees therefore are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

**This Brief is transmitted in triplicate. [37 C.F.R. § 41.37(c)].**

This Brief contains these items under the following headings and in the order set forth below [37 C.F.R. § 41.37(c)]:

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**I. REAL PARTY IN INTEREST**

The real party in interest is Dr. Gabriele Multhoff.

**II. RELATED APPEALS AND INTERFERENCES**

There are no known related appeals or interferences known to Appellants, Appellants' legal representative, or the Assignee.

**III. STATUS OF CLAIMS**

Claims 1 - 30 were filed in the original application, a National Phase Entry from PCT Application EP99/02165. During prosecution of the application, Claims 31 –87 were added, Claims 1-48, 50-60, and 78-82 cancelled, and claim 49 withdrawn. Claims 61-77 and 83-87 are currently pending and have been rejected by the Office in the Final Office Action dated April 4, 2006. Therefore, Claims 61-77 and 83-87 are pending in this appeal. No other claims are pending. Thus, Appellants appeal the Final Office Action of April 4, 2006. The Claims, as they now stand, are set forth in the Claims Appendix.

#### **IV. STATUS OF AMENDMENTS**

Appellants' Response to the Office Action mailed March 1, 2006 has been entered per the Final Office Action dated April 4, 2006. Amendments to the claims that were made in the March 1, 2006 Response were acknowledged in the Final Office Action dated April 4, 2006. Thus, there are no pending amendments not entered into the record.

#### **V. SUMMARY OF CLAIMED SUBJECT MATTER**

This invention relates to the use of Hsp70 polypeptides to activate Natural Killer Cells (NK-cells) ex vivo. See, English Translation of PCT Application at page 1, lines 9-13, and Examples 1 and 2. In particular, the invention relates to the use of a protein, protein fragment, or polypeptide selected from the group consisting of a Hsp70 protein of SEQ ID NO.: 1, a C-terminal fragment of Hsp70, wherein said fragment comprises amino acids 384-641 of SEQ ID NO.: 1, and a polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO.: 1. Id. at page 2, line 25 through page 3, line 11, and Examples 1 and 2. Preferably, the protein, fragment, or polypeptide induces an immune response by the treated NK cells. Id. at page 5, line 35 through page 6, line 8, and Examples 1 and 2. Preferably, the immune response increases cytolytic activity of the NK cells or stimulates proliferation of the NK cells. Id., and Example 2. The Hsp70 polypeptides are added to a physiological suspension containing NK cells, such as a peripheral mononuclear blood cell fraction. Id. at page 14, line 20 through page 16, line 17, and Examples 1 and 2. The cell suspension can contain diseased cells, including leukemia cells, lymphoma cells, tumor cells, metastasizing cells of solid tumors and cells from a virally, mycotically and/or bacterially infected patient. Id. at page 5, line 35 through page 6, line 8; page 16, line 19 through page 17, line 23, and Example 2. The NK-cells are thereby induced to attack Hsp70 expressing diseased cells, such as tumor cells. Id. at page 16, line 19 through page 18, line 8 (Examples 2 and 3).

**VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

There is one ground of rejection to be reviewed on appeal:

**Issue 1** – Whether Claims 61-77 and 83-87 are properly rejected under 35 U.S.C. §112(1)

for lacking adequate written description.

**VII. ARGUMENT****Issue 1 - Claims 61-77 and 83-87 are supported by an adequate written description.**

Claims 61-77 and 83-87 are rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking an adequate written description. As explained below, the Examiner's rejection is unsupportable because 1) Eli Lilly and related cases are not controlling and 2) the Examiner has ignored the Written Description Guidelines promulgated by the Office.

**1. Eli Lilly is not controlling**

The Examiner's rejection relies heavily on Eli Lilly and related cases. Final Office Action dated April 4, 2006 at p. 3-4. The Examiner states that "the Federal Circuit held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus." Id. at 3. The Examiner goes on to state "by analogy, a generic statement that defines a genus of polypeptides having 70% or greater homology to amino acids 384-641 of SEQ ID NO.:1 by only their common ability to induce an immune response by NK cells, wherein the response increases cytolytic activity of the NK cells or stimulates NK cell proliferation does not adequately describe the genus as a whole."

As a preliminary matter, Eli Lilly is not analogous as suggested by the Examiner. Neither the specification nor the claims of the patent addressed by the Federal Circuit in Eli Lilly contained the sequence for human insulin. Regents of the University of California v. Eli Lilly, 43 USPQ2d 1398 (Fed. Cir. 1997). In the instant, the sequence of a Hsp70 is provided in the both the specification and the claims and, as described in more detail below, was well known in the art as of the priority date of the application. Thus, applicants have not attempted to define a genus of nucleic acids by only their functional activity. Instead, applicants have disclosed and referred to specific sequences. Thus, the analogy the Examiner attempts to draw has no merit.

The Examiner next cites Noelle v. Lederman for the proposition that “the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species other than those specifically enumerated.” Final Office Action at 4. However, Noelle dealt with an application in which the claims were directed to monoclonal antibodies and in which only a single monoclonal antibody epitope was disclosed. Noelle v. Lederman, 69 USPQ2d 1508 (Fed. Cir. 2004). Noelle did not address the situation where specific sequences are provided in the application and claims and known in the art. Thus, Noelle is not applicable to the instant case either.

The Examiner does admit that “Applicants have pointed to several species of HSPs that may fall within the genus of at least 70% homologous to amino acids 384-641 of SEQ ID NO:1.” Final Office Action at 4. The Examiner also does not dispute, and simply dismisses the evidence provided by Applicants, that Milner and Campbell and Multhoff et al. teach that sequences within the claimed genus were known in the art. Id. at 3. In fact, the Examiner appears to accept that Milner and Campbell “teaches Hsp70-Hom and Hsp70-B both of which are at least 70% homologous to amino acids 384-641” and that Multhoff et al. “provides an overview of the Hsp70 multigene family.” Id.

For the convenience of the Office, a copy of the Milner and Campbell reference is provided herewith. As demonstrated in Example 1 and shown in Fig. 1A of the present application, the proliferation and thus activity of NK cells could be stimulated by recombinant human Hsp70 as well as by the C-terminal fragment of homologous protein rHsp70homC (see, also, the Specification at page 16, line 2 through the completion of the second full paragraph).

Thus, the Applicants have actually reduced to practice a sequence that is 70% or greater in homology to amino acids 384-641 of SEQ ID NO: 1. Furthermore, the enclosed Milner and Campbell reference provides evidence that already in 1990, i.e. eight years prior to the effective filing date of the present application, several members of the Hsp70 family were known, which can be used in accordance with the teaching of the present invention.

For example, besides the Hsp70-Hom protein the Milner and Campbell reference discloses in Fig. 4 another homologous Hsp70 protein, i.e. Hsp70-B', the amino acid sequence of which has a homology of about 74% to amino acids 384-641 of the reference Hsp70 protein. Furthermore, reference is made to the publications by the inventor Multhoff et al., Cell Stress &

Chaperones 1 (1996), 6-1 1 and Multhoff et al., Biol. Chem. 379 (1998), 295-300, both referenced at Page 1 of the present application, which provide an overview concerning Hsp70 multigene family including various citations. Thus, besides the fact that applicant actually reduced to practice homologous sequences of amino acids 384-641 of SEQ ID NO: 1 the prior art at the time the application was filed provided already a vast source of the genus of Hsp70 sequences that are encompassed in the claimed method.

In this respect, the Examiner's attention is respectfully directed to the Federal Circuit's recent holding in Falkner v. Inglis, 448 F.3d 1357; 79 U.S.P.Q.2D (BNA) 1001 (Fed. Cir. 2006). In that case, the Federal Circuit specifically held that "Eli Lilly does not set forth a per se rule that whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art." Id. at 1367. The Federal Circuit went on to explain that:

Thus, "[w]hen the prior art includes the nucleotide information, precedent does not set a per se rule that the information must be determined afresh." Id. at 1358. Rather, we explained that:

The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

Id. at 1357.

Indeed, a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention. As we stated in Capon, "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." Id. at 1358. Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification.

Id. at 1367-68. The Federal Circuit then specifically held that "where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require

either the recitation or incorporation by reference (where permitted) of such genes and sequences.” Id. In the instant case, sequences within the claims were known in the art and reference sequences were described in the specification and identified in the claims. That is all the written description that is needed.

Additionally, Applicants note that the priority date for the present application is March 27, 1998. The priority date for the patent addressed by the Federal Circuit in Eli Lilly was September 12, 1979 (i.e., U.S. Pat. No. 4,431,740). Regents of the Univ. of California v. Eli Lilly, 119 F.3d 1559, 1562 (Fed. Cir. 1997). As held by the Federal Circuit in Falkner, “Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.” Falkner, 448 F.3d at 1367-68. Surely, the state of art molecular biology had advanced considerably in the approximately 20 years elapsed between the filing the patent at issue in Eli Lilly and the present application. The simple fact is that the macromolecules utilized in the instant claims were both known when the application was filed and described in detail in the application itself. These sequences are representative of a broader genus, which any person of skill in the art can identify. Indeed, even if a person skilled in the art did not want to rely on the available Hsp70 protein species available at the time the present application was filed, the specification provides sufficient guidance how to produce and test appropriate derivatives of the exemplified Hsp70 protein and fragments thereof (see, e.g., the Specification at Page 3, second to fourth full paragraphs, Page 4, the paragraph bridging to Page 5 and Example 1 which describes spanning experiments for testing the capability of Hsp70 species to increase the proliferation of NK cells).

**2. Application of the Written Description Guidelines compels allowance of the claims**

Applicants respectfully refer the Examiner to the USPTO’s “Synopsis of Application of Written Description Guidelines”, and in particular to Example 14, pages 53-55. Consideration of the Examples in the Written Description Guidelines establishes that the claims are supported by an adequate written description.

The claim of Example 14 of the Written Description Guidelines recites a protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A->B. The disclosure of Example 14 provides a single species (SEQ ID NO:3)

that has actually been reduced to practice, and describes an assay for identifying the variants having the desired catalytic activity. The analysis considers (1) whether the members of genus vary substantially from each other; and (2) whether the disclosed species is representative of the members of the genus; in order to determine whether one of skill in the art would determine if the applicant was in possession of the necessary common attributes possessed by the members of the genus.

For Example 14, it was determined that the member species did not substantially vary since the variants have 95% identity or greater to the reference sequence, and also possess the catalytic activity. It was also determined that the disclosed species was representative since all members must have at least 95% structural identity to SEQ ID NO:3. The analysis determined that one of skill in the art would conclude that the applicant was in possession of the necessary common attributes possessed by the members of the genus, and therefore the disclosure in this Example meets the written description requirement.

Applicants submit that the instant claims can be analyzed in a similar manner to that provided in Example 14. First, the polypeptides do not substantially vary as members of a genus since they all have at least 70% homology to SEQ ID NO:1 and must possess the activity of inducing an immune response by NK cells. Second, the polypeptide having SEQ ID NO:1 is a representative species of the genus since all polypeptides must have at least 70% homology to this sequence. Therefore, one of skill in the art would conclude that the Applicants were in possession of the necessary common attributes possessed by the members of the genus, and therefore the instant specification meets the written description requirement for these claims.

The Examiner seems to attempt to draw a distinction between the 70% limitation in the present claims and the 95% homology limitation in Example 14. However, this distinction is without meaning. The Written Description Guidelines focus on the provision of a reference sequence and a limitation as to function. Both of these limitations are present in the instant claims. As a result, the Written Description Guidelines are persuasive authority that the instant claims are allowable.

### VIII. CLAIMS APPENDIX

1-48. (Cancelled)

49. (Withdrawn)

50-60. (Cancelled)

61. (Previously presented) A method for the ex vivo activation of NK- cells, comprising: contacting NK cells in physiological suspension with an isolated and uncomplexed protein, protein fragment, or polypeptide selected from the group consisting of a Hsp70 protein of SEQ ID NO.: 1, a C-terminal fragment of Hsp70, wherein said fragment comprises amino acids 384-641 of SEQ ID NO.: 1, and a polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO.: 1, wherein said isolated protein, fragment, or polypeptide induce an immune response by NK cells, and further said response increases cytolytic activity of the NK cells or stimulates proliferation of the NK cells.

62. (Previously presented) The method of claim 61, wherein said activation of said cells further comprises stimulation of proliferation and/or an increase in cytotoxicity.

63. (Previously presented) The method of claim 61, wherein said physiological suspension containing NK cells comprises a peripheral mononuclear blood cell fraction or fractions thereof.

64. (Previously presented) The method of claim 61, wherein said suspension further comprises cells expressing cell-surface Hsp70.

65. (Previously presented) The method of claim 64, wherein said expressing cells comprise diseased cells from a patient.

66. (Previously presented) The method of claim 65, wherein said diseased cells are selected from the group consisting of leukemia cells, lymphoma cells, tumor cells, metastasizing cells of solid tumors and cells from a virally, mycotically and/or bacterially infected patient.
67. (Previously presented) The method of any one of Claims 61-66, wherein said contacting is carried out for at least 3 hours.
68. (Previously presented) The method of claim 67, wherein said contacting is carried out for 4 days.
69. (Previously presented) The method of claim 67, wherein said contacting further comprise addition of cytokine.
70. (Previously presented) The method of claim 69, wherein the cytokine is an interleukin.
71. (Previously presented) The method of claim 70, wherein said interleukin is selected from the group consisting of IL-2, IL-12 and IL-15.
72. (Previously presented) A method for the in vivo activation of the immune system in a patient in need thereof comprising:
- i) administering to said patient a pharmaceutically effective amount of NK cells obtained by the method of claim 61; and
  - ii) optionally administering to said patient, concurrently or subsequently, a pharmaceutically effective amount of an isolated and uncomplexed protein, protein fragment, or polypeptide selected from the group consisting of a Hsp70 protein of SEQ ID NO: 1, a C-terminal fragment of Hsp70, wherein said fragment comprises amino acids 384-641 of SEQ ID NO.: 1, and a polypeptide having 70% or greater homology to amino acids

384-641 of SEQ ID NO.: 1, wherein said isolated protein, fragment, or polypeptide induces an immune response by NK cells, and wherein said response increases cytolytic activity of the NK cells or stimulates proliferation of the NK cells.

73. (Previously presented) The method of claim 72, where said patient is suffering from a disease selected from the group consisting if cancerous, infectious and autoimmune disease.

74. (Previously presented) The method of claim 72, further comprising administering a cytokine.

75. (Previously presented) The method of claim 74, wherein said cytokine is an interleukin.

76. (Previously presented) The method of claim 75, wherein said interleukin is selected from the group consisting of IL-2, IL-12 and IL-15.

77. (Previously presented) The method of claim 73, wherein said cancerous disease is selected from the group consisting of tumors, solid tumors, metastatic tumors, leukemias and lymphomas.

78-82. (Canceled).

83. (Previously presented) A method for in vivo activation of the immune system in a patient in need thereof comprising administering to said patient a pharmaceutically effective amount of an isolated and uncomplexed protein, protein fragment, or polypeptide selected from the group consisting of a Hsp70 protein of SEQ ID NO.:1, a C-terminal fragment of Hsp70, wherein said fragment comprises amino acids 384-641 of SEQ ID NO.: 1, and a polypeptide having 70% or greater homology to amino acids 384-641 of SEQ ID NO.: 1; wherein said isolated protein, fragment, or polypeptide induces an immune response by NK cells, and wherein

said response increases cytolytic activity of the NK cells or stimulates proliferation of the NK cells.

84. (Previously presented) The method of claim 83, where said patient is suffering from a disease selected from the group consisting of cancerous, infectious and autoimmune disease.

85. (Previously presented) The method of claim 83, further comprising administering a cytokine.

86. (Previously presented) The method of claim 85, wherein said cytokine is an interleukin.

87. (Previously presented) The method of claim 86, wherein said interleukin is selected from the group consisting of IL-2, IL-12 and IL-15.

## **IX. EVIDENCE APPENDIX**

Per 37 C.F.R. §41.37(c)(ix), a copy of Milner and Campbell, Structure and expression of the three MHC-linked HSP70 genes, Immunogenetics 32:242-251 (1990) is provided with the present appeal brief.

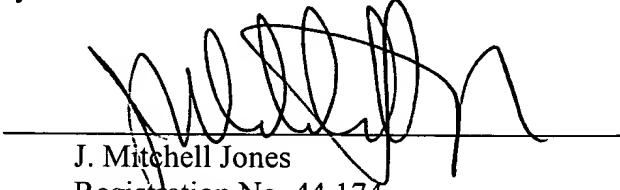
**X. RELATED PROCEEDINGS APPENDIX**

There are no related proceedings.

**XI. CONCLUSION**

For the foregoing reasons, it is submitted that the Office's rejection of Claims 61-77 and 83-87 is erroneous, and reversal of the rejection is respectfully requested. Appellant requests either that the Board render a decision as to the allowability of the claims, or alternatively, that the application be remanded for reconsideration by the Office.

Dated: January 4, 2007

  
J. Mitchell Jones  
Registration No. 44,174

MEDLEN & CARROLL, LLP  
101 Howard St., Ste. 350  
San Francisco, CA 94105  
415-904-6500